

November 23, 1956

Dr. J. J. Weigle
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California Institute of Technology
Pasadena 4, Calif.

Dear Dr. Weigle:

Thank you for sending your manuscript on lambda-Gal studies. The paper you asked about has just appeared in the Sept. 1956 Genetics; you will receive a reprint at the earliest opportunity.

Fortunately, Dr. Morse who is now working at Denver (c/o Dept. Biophysics, Univ. Colo. Med. School, Denver 20, Colo.) was visiting us yesterday, so we could discuss your note together and reply for all of us.

Morse, my wife Esther, and I are continuing the collaboration, and have already been studying some of the aspects reported in your note; others are in a different direction. Dr. Morse has been particularly concerned with the growth of lambda (in induced haploids and heterogenotes respectively) and is now assembling his data for publication. Together, we have been working on other aspects of the exogenote-prophage relationship, and want to perfect some of the details before publishing (as promised in the Genetics articles). Some of these are given in the attached summary.

As to growth and induction, in a number of experiments, Morse finds a very low yield of Gal+ per yielder (approximating 1) both for haploid (LFT⁺) and syngenetic (HFT⁺) stocks. However, the former give bursts of lambda of 50-100; the latter are again low, not much more than one. [Some caution is needed here owing to segregation; every syngenetic culture contains a few percent at least of segregants.] We do not know how to account for the discrepancy with your bursts of 15 or more Gal+ and 100 lambda per induced heterogenote, but there are some obvious variables in the experimental details, including especially the type of lambda (we assume this is the one called lambda-26 in some earlier discussions) and the media used.

We have had no unequivocal results on the increase of Gal+ from HFT lambda grown on sensitive hosts; most of the trials were, in any case, with Gal⁻ Lp^s hosts. Your result is, of course, a most important and interesting one; a number of possible interpretations of the inability of Gal⁻ hosts to give such an increase must have occurred to you. These can probably be easiest decided by growing Gal_a⁻ Gal_b⁺ phage on an A+B- host. You already know that b+ will not increase; what about a+? If it also does not grow, there is clearly a new type of interaction, perhaps akin to some of the mutual recovery interactions which Atwood has found in irradiation macroconidia of Neurospora (and, if I venture to say it in ignorance of present dogma, in multiplicity reactivation in phage). If it does, it presumably means that the endogenote is somehow being induced, although it was initially Lp^s. We have been a little suspicious of the experiment of our table 7 on the preferential

incorporation of the exogenote into HFT phage; the incidence of the endogenetic marker may or may not be fully accountable for by the frequency of autotictic types. The experiment just mentioned should be done with various a,b combinations of known positional effect (cistronic) relationships.

Dr. Morse is very anxious to repeat these findings, as they have a very close bearing on our own experiments. He will doubtless communicate with you further.

Naturally we are anxious to remain in touch with you on your further work. While, as you can see, our interests overlap on a number of issues, we will be very happy to furnish whatever materials you specify.: just indicate precisely what you want from our published descriptions, or give us enough detail that we can judge ourselves what genotypes would be most appropriate, e.g., in regard to other markers. Since we are scattered from Madison to Denver, it would be very helpful if you could communicate in duplicate, or indicate whether we should forward copies. The interesting, and we hope instructive, discrepancy in our findings on exogenote replication, on the one hand, and the behavior of Lprs on the other, indicates that some duplication of effort is not altogether wasteful.

I speak for all three of us in thanking you for the communication, in hoping we can meet sometime, and in best personal wishes.

Yours sincerely,

Joshua Lederberg
Professor of Genetics

P.S. If your note is being submitted for publication, may I ask to what journal, and whether I can cite it in a review I am preparing?

P.P.S. Many of the data in the attached brief are a year or two old, but we have held back on publishing them until we had a more coherent picture.

Table 1

Lp status of transductional progeny

Form: $\text{Gal}_1^- \text{Gal}_2^+ \text{Lp}^x \text{---}x \text{Gal}_1^+ \text{Gal}_2^- \text{Lp}^y$

	Donor x Lp:	---x Recipient y Lp:	Types of heterogenote isolated, Lp:	Types of Gal^- segregants Homogenotic Lp:	Haploid Lp:
1.	+	+	+	+	+
2.	+	s	+ rs (segregating immune) (no s, no r)	+ rs <u>only</u>	+ s <u>only</u>
3.	h	+	+ h	+	+
4.	h	s	h rs	h rs	h s
5.	+	r	r +/r rare +	r	r +, r

h refers to Appleyard's host-range mutant. (A. et al, Virology, 2:565, 1956)

r refers to "defective prophage" mutants.

rs refers to immune types which invariably segregate s, and not r.

6.	+	RS ($\text{Gal}^-/\text{ex Gal}^-$)	? +/rs = +/s/s	+, rs	+, s
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Initially we were surprised that Lp did not segregate in coupling with Gal (experiments 2, 3, 4 above) as it does in heterozygotes. The origin of the immune response of rs types was also puzzling. The data are consistent with the proposals 1) that the primary syngenote after transduction undergoes a process of obligatory homogenosis for the Lp factor, Lp^+/ Lp^s thereby giving either Lp^+/ Lp^+ or Lp^s/ Lp^s ; 2) that the rs phenotypes correspond to the latter. This might mean that the Lp^s factor interferes with lysis by lambda ~~mutant~~ when Lp^s is exogenotic, or at least that an exogenote confers the rs phenotype in association with an Lp^s endogenote.

The above experiments are still somewhat tentative; most attention is being given to the exploration of $\text{Lp}^+ \text{---}x \text{Lp}^s$, ~~mutant~~ and to rare cases of h/+ progeny, which so far furnish the most direct evidence for ~~heterogenosis~~ heterogenosis for Lp.

A variety of crosses have been done which show that 1) the transfer of exogenotes via conjugation gives the same basic results as in phage-transduction; 2) the exogenote tends to be "linked" to the endogenote in transduction. Analogous experiments with P1-transduction are just getting started. crossing

Some exceptions to the above patterns have been found, especially after UV-treatment of the phage, but they do not invalidate the generality of the results. Other kinds of experiments (e.g., segregation in the primary transduction clones) have also been done and are being continued.